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Case studies

Restless leg syndrome manifested by iron deficiency from chronic hemoptysis in cystic fibrosis

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Abstract

Restless leg syndrome (RLS) and periodic limb movement disorder (PLMD) are considered to be a continuum of a neurological sleep disorder associated with abnormal iron metabolism or deficiency. I describe a case of RLS and PLMD in a cystic fibrosis patient with iron deficiency from chronic hemoptysis. This is the first case that reports RLS and PLMD manifesting from iron deficiency caused by chronic hemoptysis in advanced cystic fibrosis lung disease.

Keywords: Cystic fibrosis; End stage lung disease; Restless leg syndrome; Periodic limb movement disorder; Iron deficiency; Hemoptysis

1. Introduction

Restless leg syndrome (RLS) and periodic limb movement disorder (PLMD) are closely related disorders that are considered to be a continuum of the same disorder that can disturb sleep onset and sleep maintenance. RLS is a clinical diagnosis during waking hours, and PLMD is a sleep disorder with clinical symptoms of excessive daytime sleepiness or insomnia requiring nocturnal polysomnography (NPSG) for diagnosis. The criteria for diagnosis of RLS include 4 primary features: (1) unpleasant limb sensations with desire to move the limbs usually associated with paresthesias/dysesthesias; (2) motor restlessness, with the patient feeling compelled to move; (3) symptoms precipitated by rest and relieved by activity; and (4) symptoms worse in the evening or at night [1]. RLS affects approximately 10% of the population, prevalence increasing with age [2]. The limb movements of PLMD are defined as repetitive, stereotypical dorsiflexions of the great toe with fanning of the small toes accompanied by flexion of the ankle and knee occurring at 5 to 90 second intervals with duration of 0.5 to 5 s [3]. At least four of these movements must be present to meet NPSG criteria for a single periodic limb movement [3]. The International Classification of Sleep Disorders (ICSD) endorses a grading system for severity of PLMD: a PLM index of <5/h is considered normal, 5–24/h mild, 25–49/h moderate, and ≥ 50/h severe [4]. The ICSD further reports that the diagnosis of PLMD requires symptoms of excessive daytime sleepiness and/or insomnia in the presence of a positive NPSG without evidence of a medical or psychiatric disorder that could account for complaints [4].

Familial RLS is described with 63% of RLS patients ($n=127$) reporting the presence of RLS in at least one of their first-degree relatives [5]. Patients with hereditary RLS have a significantly younger age of onset of disease than those with a negative family history [6]. The pathophysiology of primary RLS is associated with dopaminergic dysfunction and abnormal brain iron metabolism, and secondary RLS is commonly associated with iron deficiency [7]. Iron deficiency is a significant concern in the cystic fibrosis (CF) population with progressing lung disease being associated with iron loss in sputum [8]. Iron deficiency in the CF population is not related to pancreatic insufficiency or its supplementation [9,10]. I

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describe a case of RLS/PLMD resulting from iron deficiency in a CF patient with end stage lung disease and chronic hemoptysis.

2. Case report

22-year-old male with CF and pancreatic insufficiency presented to the adult CF clinic for routine care. Due to end stage lung disease and deteriorating pulmonary function, he was started on supplemental oxygen at 2 L per minute during exercise and sleep and was listed for lung transplantation 1 year earlier. For the past 6 years, he had daily cough productive of green sputum. He developed the onset of small streaks of blood in his sputum 2 years previous. The hemoptysis initially occurred monthly; but over the past 6 months, the frequency of episodes had increased to daily. The volume of blood loss described as less than a teaspoon per episode had not changed. His appetite was excellent with supplemental gastrostomy tube feeds overnight. He denied abdominal pain, nausea, vomiting, heartburn, gastroesophageal reflux, hematemesis, melena, and hematochezia. He denied use of iron supplements as well as reported that he rarely consumed red meat. He was diagnosed with depression 1 year previous but refused medical therapy. For the past 18 months, he had noticed daytime fatigue and hypersomnolence with progression of these symptoms over the past 6 months. Despite 7 to 8 h of sleep nightly, he reported awakening with non-restorative sleep. His wife confirmed that he kicked his legs and jerked his lower body throughout the night. Further questioning revealed that he had an occasional urge to move his legs during the day with worsening of this sensation prior to bedtime leading to difficulty achieving sleep. This urge to move his lower extremities was not associated with pain but rather a sensation of "pins and needles," with resolution of the symptoms upon walking. He denied arm involvement but reported that symptoms occurred in both legs with daytime naps. Kidney and liver function was normal, and screening for cystic fibrosis related diabetes was unremarkable. He further denied history of esophageal varices and peripheral neuropathy as well as family history of RLS/PLMD.

Physical exam of both lower extremities was normal without skin discolorations or hair loss and normal pulses. Complete neurological exam was normal with intact gait. His pulmonary function was at baseline with FVC of 2.27 L (44% predicted) and FEV [1] of 1.17 L (28% predicted). Chest X-ray revealed chronic changes related to CF and significant hyperinflation. Laboratory findings revealed hemoglobin 14.4 g/dL (13.6–17.2 g/dL), mean corpuscular volume (MCV) of 79 fL/RBC (82–97 fL/RBC), iron level of 13 μg/dL (50–160 μg/dL), transferrin saturation of 3% (16–50%), and ferritin level of 32 μg/L (20–300 μg/L). Stools were negative for blood. Cell count of sputum cultures obtained over the past 2 years had >25 red blood cells/low power field consistent with chronic blood loss in his sputum confirming his observations of chronic hemopytsis in his sputum. To assess for PLMD and other sleep disorders, a NPSG revealed normal sleep and rapid eye movement (REM) latencies with a significantly reduced sleep efficiency at 62%. Ten hypopneas lead to an apnea–hypopnea index of 2.3 events per hour of sleep on supplemental oxygen at 2 L per minute. A total of 93 limb movements met criteria for PLMD leading to an arousal index of 19 events per hour of sleep. Supplemental ferrous sulfate of 300 mg orally twice daily was initiated with continuation of supplemental oxygen. With the iron supplementation, symptoms of RLS during the day and PLMD during sleep resolved over the next month leading to significant improvement in daytime fatigue and hypersomnolence. At follow up 3 months later, his iron indices had normalized.

3. Discussion

The mechanism of action of primary or idiopathic RLS is not completely understood; however, a recent study indicates that RLS may be due to low brain iron concentration caused by the dysfunction of iron transportation from serum to the central nervous system [10]. Several etiologies are associated with secondary RLS; including iron deficiency, renal failure, neuropathies, myopathies, pregnancy, and drugs (caffeine, serotonin reuptake inhibitors, tricyclic antidepressants, and dopamine blockers) [1]. The rationale for iron deficiency involvement of these disorders is the need for iron in tyrosine hydroxylation which is the rate limiting step in the biosynthesis of dopamine. Magnetic resonance imaging (MRI) techniques have demonstrated decreased iron content in the nigrostriatal areas in RLS patients [11]. Disease severity correlates the degree of nigrostriatal iron depletion [11]. Sun et al. published that RLS is exacerbated with ferritin levels <50 μg/L [12]. Reduced ferritin and elevated transferrin levels in cerebrospinal fluid is indicative of low brain iron in patients with idiopathic RLS [13].

Iron deficiency has been described in the CF population [8,9,14]. A study of 127 patients revealed 32% having low serum ferritin concentrations and iron deficiency [14]. Pond and colleagues reported 62% of adult CF patients ($n=71$) had functional iron deficiency defined as transferrin saturation <16% with 12 patients being anemic (10 with iron deficiency and 2 with normal iron studies) [9]. Of the 30 randomly selected adult CF patients (median age, 26 years; range, 21 to 36 years), 74% had iron deficiency defined as serum iron levels ≤12 μmol/L and/or transferrin saturation ≤16% [6]. In 2002, Reid et al. published that CF patients are iron deficient due to loss of iron within the airways [8]. Median serum ferritin levels were 39 μg/L with a range from 5 to 440 μg/L with sputum concentrations of iron (median, 63 μmol/L; range, 17 to 134 μmol/L) and ferritin (median, 5038 μg/L; range 894 to 6982 μg/L) [8]. There was a significant negative relationship between lung function measured by FEV[1] percent predicted and sputum iron and ferritin content [8].

If iron deficiency is not the cause of RLS/PLMD or if there is no response to iron replacement, commonly used drug therapies for RLS/PLMD include dopaminergic agents

(carbidopa–levodopa), dopamine agonists (pergolide, parmipexole, and ropinirole), benzodiazepines, antiepileptics, and opioids [15]. Treatment should be individualized with consideration of behavioral therapy if indicated.

4. Conclusion

In addition to iron deficiency, other factors may contribute to the development of RLS/PLMD as it is clear that not all patients with iron deficiency develop RLS/PLMD; and conversely, this disorder continuum may occur in patients without iron deficiency. However, iron deficiency is a significant aggravator of this disorder in those patients susceptible for either genetic or systemic reasons. Advanced CF lung disease is a risk factor for iron deficiency due poor nutritional status, loss of blood due to esophageal varices from liver disease if present, and iron loss into airway secretions. As their lung disease progresses, CF patients may suffer from significant fatigue with advancing lung disease being the most likely etiology; however, other contributing factors should also be considered. Physicians should be aware of RLS/PLMD as a potential contributing factor to fatigue and hypersomnolence in this patient population.

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